BCG, Latitude, and Environmental Mycobacteria

To the Editor—The systematic review of protection by BCG provides useful clarification of factors that explain the wide range of efficacy reported in randomized trials and will help inform design of trials of new vaccines against tuberculosis [1]. The conclusions regarding the role of BCG strain variation (no effect) and prior exposure to environmental bacteria (reduced efficacy) are based on a sound analysis of existing studies, but the interpretation of the role of latitude is confounded.

The problem is that the efficacy of BCG is greatest in mycobacteria-naive infants and that the only well-designed prospective studies in infants have been conducted in the north. Thus, someone comparing studies from equatorial regions with those from the north will necessarily, but wrongly, conclude that latitude is a determinant of efficacy. The 4 well-designed prospective studies in newborns and infants showed a collective efficacy of 73% against disease and 87% against death, and were all conducted in the north [2]. No comparable studies have been conducted in equatorial latitudes: the South India trial did not include significant numbers of mycobacteria-naive infants [3], and the Mumbai infant trial included in the review does not meet acceptable trial standards for randomization, blinding, and case ascertainment [4]. Unless transplacental factors in tuberculosis-endemic countries prove to influence infant BCG efficacy it should not be assumed that infant BCG immunization will be any less effective in equatorial regions than in the north.

Another point considered in the review deserves comment. It is commonly stated that infections with environmental non-tuberculous mycobacteria (NTM) are more common in equatorial than northern regions. However, data from environmental sampling, skin test studies, antibody surveys and rates of overt disease indicate otherwise. The highest environmental recovery rates of NTM ever reported are from a study in Finland where 100% of samples were positive [5]. Dual skin test studies with purified protein derivative and a well-standardized NTM antigen using identical methods at all sites showed no difference in rates of NTM infection among healthy volunteers in the United States, Finland, Kenya, and Trinidad [6]. Children in the United States, where tuberculosis is uncommon, have increasing rates of antibody to mycobacterial lipoprotein-mannan with age, with 96% of 15–18-year-olds positive [7]. Colonization of circulating hot water systems with NTM is common in the United States and is likely to expose most healthy adults [8]. Finally, pulmonary and disseminated disease due to NTM is much less common in equatorial regions than in the north [9,10]. The important difference in prior mycobacterial sensitization between north and south is the high rate of latent Mycobacterium tuberculosis in tuberculosis-endemic countries in the south.

There are 2 important messages for trials of new tuberculosis vaccines: (1) controlled trials of new priming vaccines to replace BCG in mycobacteria-naive infants should be based on an expected efficacy of >70% for BCG in any region of the world; and (2) because most adolescents and adults throughout the world will have had prior mycobacterial sensitization, live, subunit, or inactivated vaccines should be capable of boosting preexisting mycobacterial immune responses.

Note

Potential conflicts of interest. Author certifies no potential conflicts of interest.

The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

C. Fordham von Reyn
Infectious Disease and International Health, Dartmouth-Hitchcock Medical Center, Geisel School of Medicine, Hanover, NH, USA

References
